

# Pediatric INSIGHTS

## In This Issue

Sequential Lung and Stem Cell Transplantation  
New Recruit  
Video Rounds and Online CME  
Pediatric Heart and Lung Transplantation  
Recognition and Awards  
Recent Publications

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An Update From the Division of Pulmonary Medicine, Allergy, and Immunology

## A PATIENT WITH SEQUENTIAL LUNG AND STEM CELL TRANSPLANTATION



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A.B. was 11 years old with IL-7 receptor mutation leading to severe combined immunodeficiency (SCID) when she first presented to Children's Hospital of Pittsburgh of UPMC. She was referred to Pulmonology for lung transplant evaluation due to severe bronchiectasis secondary to chronic and recurrent lung infections. At the time of presentation, she was chronically hypoxemic, requiring oxygen on a continuous basis. She had difficulty walking short distances and often required a wheelchair. She had additional symptoms of wheezing, cough, and persistent sputum production

requiring mucus clearance techniques and ipratropium, albuterol, and budesonide. Due to recurrent infections, she was prescribed chronic inhaled antibiotics as well as IV antifungals. She was known to grow a resistant strain of *Alcaligenes*, sensitive only to carbapenems. She also received intravenous immunoglobulin (IVIG) and rituximab. On presentation, with nasal cannula oxygen, she was noted to be slightly cyanotic. She had signs of increased work of breathing, including suprasternal and intercostal retractions. Lung exam revealed mild hyperinflation and fair air exchange, somewhat diminished at the bases. There were diffuse, wet mid-to-late inspiratory crackles. She also had mild-moderate digital clubbing.

Spirometry revealed an FEV1 of 18%. During her six-minute walk test she was able to walk 80 meters (12% predicted). Chest CT confirmed that bronchiectasis was bilateral, affecting all lobes. Prior lung biopsy revealed nonspecific findings.

*Continued on Page 2*



**Figure 1:** CT scan of chest at the time of presentation.



**Figure 2:** CT scan of chest after transplantation.

## SEQUENTIAL LUNG AND STEM CELL TRANSPLANTATION

*Continued from Page 1*

These collective findings confirmed that A.B. was an appropriate candidate for lung transplantation due to end-stage lung disease secondary to recurrent pneumonias from



her underlying immunodeficiency. However, the concern was that transplanted lungs would suffer the same fate as her native lungs and eventually develop bronchiectasis from chronic and recurrent infection.

A.B.'s IL-7 receptor mutation resulted in minimal CD3+ T cell development. This was confirmed by low CD4+ and CD3+ counts. Because her lung disease was so progressive, bone marrow transplantation (BMT) could not be recommended. This is ideally done prior to the development of lung disease. Therefore, it was determined that the best course of treatment for A.B. was to have sequential lung and stem cell transplantation.

Lung transplantation can be performed without human leukocyte antigen (HLA)-matching criteria, using ABO typing, size, and lung function parameters primarily. However, for A.B., it was suggested to identify a partially HLA-matched donor to provide functional immunity by engrafting the bone marrow-derived immune system. This would hopefully prevent both rejection and graft-versus-host disease (GVHD) of the lungs. Unfortunately, host T cells can still induce rejection if they survive past the BMT conditioning regimen, and GVHD of the skin and gut are still possible. FDA and IRB approval was obtained for sequential bilateral orthotopic lung transplantation and donor-derived stem cell transplantation.

While listed for transplant, A.B.'s hypoxemia worsened, and she began to require 4 to 5 L of continuous supplemental oxygen. She also was started on BiPAP at night due to worsening hypoxemia and inability to sleep supine. Once

a suitable donor was identified with partially matched HLA, she was able to receive her lung transplant. Basiliximab and methylprednisolone were initially used for induction immunosuppression, with tacrolimus and mycophenolate initiated as maintenance therapy until successful bone marrow transplantation. She tolerated lung transplantation well, and she was discharged two weeks later breathing room air.

Post-lung transplant, A.B. had almost complete resolution of her respiratory symptoms of cough, wheeze, and sputum production. Due to chronic deconditioning, she still had some exertional limitations, but these were improving as well with physical therapy. She was noted to have impaired right hemidiaphragm movement, which resulted in restrictive lung volumes. Surveillance bronchoscopies with biopsies and BAL revealed no signs of acute cellular rejection or acute infections.

A.B. began conditioning with hydroxyurea, anti-thymocyte globulin, thiotepa, and total body irradiation in preparation for her stem cell transplantation. Four months after her bilateral lung transplant, she received a 2/6 HLA-matched cadaveric CD3/CD19 depleted bone marrow and vertebral body-derived hematopoietic stem cell transplant from the same cadaveric lung donor. Post-transplant she received granulocyte infusions and engrafted within two weeks. She was discharged with chronic immunosuppressants: tacrolimus and prednisone. Three months later, A.B. developed Grade II GVHD of the skin. This was initially managed with methylprednisone, tacrolimus, and steroid cream. Now, one year post-bone marrow transplant, A.B. is doing well. She continues on relatively low-dose tacrolimus and prednisone regimens. Due to growing *Pseudomonas* in her bronchoalveolar lavage, she is on a cycled inhaled tobramycin regimen, but otherwise A.B. has stable pulmonary function testing and continues to have no further difficulty with hypoxemia. •

## NEW RECRUIT



**Mark Dovey, MD**, will join the Division of Pulmonary Medicine, Allergy, and Immunology in March 2017 as fellowship director and associate director of the Cystic Fibrosis Center. Dr. Dovey has had a distinguished career as a clinician, educator, administrator, and leader in pediatric pulmonary medicine, most recently serving as vice-chair of pediatric clinical services at Boston Medical Center and Boston University. •

## Video Rounds

Video Rounds is a series of short, informative, and educational videos created for physicians that cover a variety of medical and surgical disciplines.

### **Cellular Mechanisms Linking Influenza to Pneumonia**

*Presented by John Alcorn, PhD*

Dr. Alcorn discusses a recent study demonstrating the connection between influenza and pneumonia, which could lead to effective clinical applications.

### **Pulmonary Function Testing in the Pediatric Population**

*Presented by Daniel Weiner, MD*

Dr. Weiner discusses how infant pulmonary function testing is no longer used solely for research and testing, but is becoming the diagnostic tool of choice in obtaining lung function data and recommending treatments.

To watch these videos or to access the full library, visit [UPMCPhysicianResources.com/VideoRounds](http://UPMCPhysicianResources.com/VideoRounds).

## Online CME

UPMC Physician Resources brings free educational CME opportunities to your computer and tablet device.

### **Childhood Obesity and Asthma: A Complicated Relationship**

*Presented by Erick Forno, MD, MPH*

Dr. Forno examines current evidence on the association between obesity and asthma in children and adolescents, discusses research developed to understand the association of obesity and asthma, and presents case examples.

To view this course or to view more resources, visit [UPMCPhysicianResources.com/Pediatrics](http://UPMCPhysicianResources.com/Pediatrics).



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## PEDIATRIC HEART AND LUNG TRANSPLANTATION

For more than three decades, Children's Hospital of Pittsburgh of UPMC has been a national leader in pediatric cardio-pulmonary transplantation, having proven its legacy of innovation with achievements in immunosuppression, ventricular assist devices (VADs), and the study of genetics and its impact on patient outcomes.

The program encompasses heart, lung, and heart-lung transplantation, including bridges to transplant such as VADs and extracorporeal membrane oxygenation. Recent clinical innovations include transplantation of highly allosensitized heart transplant candidates, and a collaboration with the Blood and Marrow Transplantation program where children suffering from immune deficiencies and severe lung disease receive a lung transplant in tandem with a bone marrow transplant.

Today, the program is led by **Geoffrey Kurland, MD**, medical director, Lung Transplant; **Brian Feingold, MD, MS**, medical director, Heart and Heart-Lung Transplant; and **Victor Morell, MD**, surgical director, Heart, Lung, and Heart-Lung Transplant.

### Outcomes

Our heart and lung transplant survival rates consistently outperform the national average and are among the world's best.

#### Pediatric Lung Transplant Survival Rates

- 1 Year: 100% (national average 87%)
- 3 Years: 80% (national average 72%)

#### Pediatric Heart Transplant Survival Rates

- 1 Year: 93% (national average 92%)
- 3 Years: 100% (national average 88%)

Sources: Internal data, Hillman Center for Pediatric Transplantation; Scientific Registry of Transplant Recipients ([www.srtr.org](http://www.srtr.org)), June 2016 release.

To refer a patient or seek a consultation, contact the Pediatric Heart and Lung Transplantation Program at 412-692-5541 (Monday through Friday, 8 a.m. to 4:30 p.m.) or 412-692-5325 (24 hours, ask for the pediatric transplant cardiologist on call). •

## ABOUT CHILDREN'S HOSPITAL OF PITTSBURGH OF UPMC

Children's Hospital of Pittsburgh of UPMC is a leader in the treatment of childhood conditions and diseases, a pioneer in the development of new and improved therapies, and a top educator of the next generation of pediatricians and pediatric subspecialists.

Children's is consistently recognized for its research and clinical achievements, including ranking 10th among children's hospitals and schools of medicine (FY15) in NIH funding for pediatric research, and being named to the 2016-17 *U.S. News & World Report* Honor Roll of America's Best Children's Hospitals.

## RECOGNITION AND AWARDS

**John F. Alcorn, PhD**, associate professor of Pediatrics at the University of Pittsburgh School of Medicine, was elected to the Society for Pediatric Research.

**Raymond A. Frizzell, PhD**, scientific director of the University of Pittsburgh Cystic Fibrosis Research Center, received the Paul di Sant'Agnese Distinguished Scientific Achievement Award from the Cystic Fibrosis Foundation, the highest scientific award the foundation bestows. •

## RECENT PUBLICATIONS

Forno E, Weiner DJ, Mullen J, Sawicki G, Kurland G, Han YY, Cloutier MM, Canino G, Weiss ST, Litonjua AA, Celedón JC. Obesity and Airway Dysanapsis in Children With and Without Asthma. *Am J Respir Crit Care Med*. 2016; Aug 23. Epub ahead of print. PMID: 27552676.

Puranik S, Forno E, Bush A, Celedón JC. Predicting Severe Asthma Exacerbations in Children. *Am J Respir Crit Care Med*. 2016; Oct 6. Epub ahead of print. PMID 27710010. •